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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/995,225	CHEN ET AL.	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,42 and 44-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,42 and 44-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/2/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/30/07 has been entered.

2. Amendment filed 10/30/07 has been entered. Claims 1-28, 30-41, 43 and 57-61 are cancelled. Applicant has amended claims 42, 44, 45, 46, 49-51 and 53-55. Claims 29, 42, 44-56 are examined as relating to the elected invention.

3. IDS filed 11/0/207 has been considered.

4. The amendment filed 10/30/07 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicant has inserted two paragraphs between line 21 and 22 on page 25 of the specification without providing support.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC 101 and 35 USC 112, 1st paragraph

The following is a quotation of 35 U.S.C. 101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 29, 42, 44-56 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reason given in the previous office action and those given below:

A specific utility is a utility that is specific to the subject matter claimed, as opposed to a general utility that would be applicable to the broad class of the invention. A "substantial utility" is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. A "well established utility" is a utility that is well known, immediately apparent, or implied by the specifications disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. A well established utility must also be specific and substantial as well as credible. Based on the record, there is not a "well established utility" for the claimed invention.

In this case, the Applicants have asserted in the instant specification that hRUP35 is **involved in motor control. Given this information, one of skill in the art would recognize that hRUP35 is useful in identifying compounds, e.g. agonists and inverse agonists, for the treatment of motor control symptoms in disorders and diseases of motor control.-----** Applicants argue given that the asserted role of hRUP35 in motor control has been confirmed by Torres et al., supra, the Applicants submit that one of skill in the art would have no reason to question the objective truth of the Applicants' statement. This rejection should be withdrawn for this reason alone. Applicants also argue the Examiner presents several lines of reasoning to counter the Applicants' assertion

of utility. In one line of reasoning, the Examiner argues that it is unreasonable to conclude that hRUP35 has a utility in motor control based on hRUP35's expression pattern. The Applicants submit, however that **Sesens et al,7** a post-filing publication, independently came to the same conclusion as the Applicants - namely that hRUP35 is involved in motor control - based on the expression pattern of the mouse homolog of hRUP35. As such, the Applicants submit the asserted utility of hRUP35 in motor control is reasonable. Apllicants argue that since Torres et al, supra, confirmed the asserted utility of hRUP35 in motor control, the Examiner's argument lacks force and merit. Applicants also argue that the Examiner counters the Applicants' position by arguing, in summary, that the Applicants allegedly do not know the exact function or ligand of hRUP35, or the exact mechanism by which hRUP35 works. The Applicants submit, however that the utility requirement under § 101 does not require that the ordinarily skilled artisan understand why the claimed subject matter is useful or the exact mechanism through which a receptor works. Instead, the skilled artisan need only be told that it is useful and how it can be used. Applicants argue they have met those burdens and that it is well established that an understanding of the scientific theory or principle underlying an invention is not a requirement for patentability. Thus, while the exact mechanism of action of hRUP35 might be an interesting topic for discussion, assertions regarding the mechanism of action of hRUP35 has no bearing on the patentability of the rejected claims.

Applicants have asserted that hRUP35 is linked to motor control. Since motor control dysfunction can appear as a symptom of a number of different diseases, modulators of hRUP35 may be employed to modulate motor function in a number of different diseases. It is argued the situation here is much akin to that of, for example, inflammation and pain where polypeptides or polynucleotides can be used to identify drugs for the treatment of these conditions. In conclusion applicant is arguing that since hRUP35 is expressed in specific regions of the brain, it is involved or linked to motor control

or as argued in Applicant's previous response, is associated with sensorimotor processing and arousal disorders.

Applicant's arguments have been fully considered but they are not found persuasive for the reasons given below:

Applicants have asserted that hRUP35 is linked to motor control but have not identified a specific motor function it is involved in and how it effects that specific motor control. Since motor control dysfunction can appear as a symptom of a number of different diseases, modulators of hRUP35 may potentially be employed to study the modulation of motor function in a number of different diseases. This is considered further experimentation to since the relationship of motor function and a disease was not known at the time of filing of instant application. When ligand binds hRUP35 does it stimulate or inhibit the specific motor function? What is the motor function, what is the dysfunction? Walking, blinking, twitching, shaking, are all motor functions. There is no indication that stimulation of hRUP35 causes a person to walk faster, while twitching, blinking and shaking. The possibility that hRUP35 would function in all these motor functions at once is not likely. Can it be tested, possibly. Has it been tested by Applicants, no it has not. Therefore, the question to ask is what does the statement "involved in motor function" mean as it relates to hRUP35. At the time of filing of instant application the involvement of hRUP35 with a specific motor function was unknown. At the time, based on the localization of hRUP35 in the brain, it was a good guess to say "involved in motor function". Further, generally stating "modulators of hRUP35 may be employed to modulate motor function in a number of different diseases" means nothing without knowing the specific disease and how hRUP35 is specifically employed to modulate that disease. The disclosure in the specification in no way leads to the conclusion drawn by Torres et al who showed GPR139 knock out mice showed impairment in balance. Walking, twitching, blinking, shaking, balance, hand movement are all motor functions, to name but a few. It is not clear how the specification links lack of GPR139 with impairment of balance?

Applicants present Abstract #328 from the February 2006 Keystone Symposium (enclosed) which discloses GPR139 knock out mice showed impairment of motor function as evaluated by using runway and open field gait analyses, retard, balance beam, and other tests. At two months of age mice showed no impairment in any of these behaviors. At five months of age the mice showed impairment in balance. The conclusion was GPR139 null mutants appear to have a primary age-related balance deficit. Based on this post filing abstract (2006) applicant have argued their invention is useful in treating motor control, sensorimotor processing and arousal disorders, such as tremor disorder, action tremor disorder, disorders of impaired motor coordination and impaired cognitive performance. In Applicant's previous response, which is incorporated into their most recent response, but not reiterated, Applicants stated, "Thus, the reference clearly substantiates Applicants' position that hRUP35 is associated with such disorders." The results disclosed in Abstract #328 were neither disclosed by applicant or could have been predicted from applicants' disclosure. How does applicants observation that hRUP35 expression in thalamus and increased IP3 levels in 293 cells lead to the prediction that mice lacking hRUP35 would have a balance deficit at five months? Applicants had no way of predicting the function based on the lack of the expression of hRUP35 gene at the time of filing instant application. Further the lack of the polynucleotide in humans had not been determined. A disease state having a dysfunction in hRUP35 that results in a balance disorder in humans has not been shown. Therefore applicant cannot use post-filing art to assert utility on their claimed invention.

All motor functions are not associated with the same disease or dysfunction. The examiner provides two references below, as examples that highlight the variability in motor functions in various diseases.

Mergl et al (Kinematical analysis of emotionally induced facial expressions: a novel tool to investigate hypomimia in patients suffering from depression, J Neurol Neurosurg Psychiatry. 2005 Jan;76(1):138-40) discloses:

A novel technique for the kinematic analysis of emotionally induced facial expressions was applied to detect subtle mimic dysfunction in patients with depression. Using ultrasound markers at certain points on the face, facial movements were exactly measured while subjects watched a witty sketch. Twenty five medicated patients with depression and 25 healthy controls were studied. Depressed patients were characterized by abnormally slow velocity at the beginning of laughing and voluntary facial movements, in addition to reduced laughing frequency. A higher severity of symptoms of depression was significantly associated with slow initial velocity of laughing movements of the left mouth angle. CONCLUSION: The execution of voluntary and non-voluntary facial movements is abnormally slow in depressed patients, reflecting hypomimia. This mimic slowing is closely associated with the severity of depression. The response of depressed patients to emotional stimuli is also abnormally low, but emotional estimation of the stimuli is similar to normals. This pattern parallels the motor-emotional features known from patients with Parkinson's disease.

Mergl further discloses in many **depressed patients, emotionally induced facial expressions are greatly reduced**. Studies have demonstrated a reduced number of facial movements in depressed patients. However, this finding is unspecific. Therefore, methods are needed that can separate the facial abnormalities in depression from those in other diseases and that can distinguish between drug induced and disease related facial abnormalities. A new computer aided method for the exact measurement of the initial velocity (IV) of laughing movements triggered by emotional (humorous) stimuli might be useful in this respect. Using kinematic analysis, Juckel *et al* separated unmediated schizophrenic patients who had an abnormally fast IV of laughing from schizophrenic patients treated with typical narcoleptics, such as haloperidol, who had an abnormally slow IV. In view of these promising results Mergl aimed to investigate facial movements elicited by humorous film stimuli in depressed patients and healthy subjects, using a computer based approach. Facial activity was expected to be abnormally reduced in depression.

Mavrogiorgou et a l(Kinematic analysis of handwriting movements in patients with obsessive-compulsive disorder *J Neurol Neurosurg Psychiatry* May, 2001;**70**:605-612) discloses:

A large range of motor disturbances is associated with OCD psychopathology, including catatonic signs, motor slowness and hyperkinesia. Abnormalities of fine motor coordination and involuntary movements—typical neurological "soft" signs—were also found in about 30% of patients with OCD. Several studies have shown that a subset of patients with OCD is characterized by an increase in these signs. Furthermore, some findings suggest that the signs may be a biological marker of a subgroup of patients with OCD with higher neuropsychiatric impairment than other patients with this disorder: patients with

OCD with more neurological soft signs had more severe obsessions and a decreased response to treatment with serotonin reuptake inhibitors. In addition, several studies suggest a lateralization of neurological soft signs to the right hemisphere.

In this study, the kinematic analysis of hand movements was used to compare the motor performance of patients with OCD with that of healthy controls. The main aim was to confirm the hypothesis that **patients with OCD write and draw slower and less automatically than controls**. Another aim was to determine if there exists a lateralization of hand motor dysfunction towards the right cerebral hemisphere in patients with OCD. If this were the case, differences between the dominant and the non-dominant hand in motor performance for velocity, consistency of velocity, and the degree of disturbances of automatisation would be expected to be significantly higher in patients with OCD than in controls. The extent to which hand movement dynamics is modulated by clinical variables (age at onset of disease, severity of obsessions, and depression) in patients with OCD was also investigated.

It is of interest to compare the kinematic profile of handwriting movements in patients with OCD with that of patients with basal ganglia disorders (Parkinson's disease (PD) and Huntington's disease (HD)), as several findings lend support to the assumption that basal ganglia dysfunction is a relevant factor in the etiology of OCD. **Patients with PD have been found to write significantly more slowly and smaller than controls**; their hand movement consistency has been reported to be normal; their acceleration phases were significantly longer than in age matched healthy subjects. **Patients with HD showed significantly lower and less consistent velocity and a tendency for less consistent stroke length while writing**. Stroke length and the skewness coefficient have been reported to be normal in HD.

The kinematic profile of handwriting movements in patients with OCD has more in common with that of patients with PD than those with HD. However, different handwriting tasks were used in the studies mentioned above: The drawing of cursives versus the writing of a sentence and a signature in this study, requiring more motor control. Therefore, it may be argued that diseases of the basal ganglia are associated with severe motor impairment in even simple tasks, whereas hand motor disturbances of patients with OCD are discrete and can only be detected by computerized methods.

The Susens reference, page 520, last paragraph, states, "The presence of GPR139 in brain areas involved in motor control suggests a function as mediator in locomotors activity. Identification of a ligand or of ligands for both receptors may help to clarify their function." Susens does not disclose the specific motor function that is associated with the GPR139. The presence of the receptor in that specific part of the brain "suggests" it has a function in

locomotors control." There is no statement that it is involved in locomotors control or what that locomotors function is. Susens further goes on to say that the identification of a ligand or ligands for this receptor **may help to clarify its function.** Susens further discloses the closest related receptor in terms of amino acid identity to GPR19 is GPR142 (page 517) and that their relatedness to other members of the rhodopsin family of GPCR was not very revealing and included peptide and chemokine receptors with identities in the range of 20-25% (table 1). GPR19 is itself an orphan GPCR. The examiner agrees that it is plausible to assume that any protein found in the motor centers of the brain can be hypothesized to be involved in motor function. The elucidation of the specific function, however, requires further research, especially in instant case where GPR19 is expressed in putamen, medulla, caudate nucleus, thalamus, amygdale and spinal cord. (see Susens page 414, column 2)

Examiner is not disputing that the claimed invention encodes a GPCR, but that said GPCR does not have a specific, substantial and credible utility. Although the claimed receptor has been shown to be expressed in the thalamus there is no disclosure of the specific association with a specific motor function, sensorimotor processing or arousal disorder. The determination of the specific association with a specific motor function, sensorimotor processing or arousal disorder requires further research. Unlike one of Applicants earlier arguments pertaining to agonists of the niacin receptor, no agonists or antagonists of RUP35 are disclosed which can be used to support a specific, substantial and credible utility. Again, the determination of said ligands and their specific use requires further research. Unlike the niacin receptor agonist, which can be used to raise HDL levels in man, no agonists or antagonists are disclosed for RUP35 which have a specific use such as raising HDL levels. When the claimed GPCR is compared to Example 12 of Revised Interim Utility Guidelines Training Materials said GPCR has no specific disclosed function or specific ligands that can be used to support utility. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the claimed hRUP35 further experimentation is necessary to attribute a utility to the claimed hRUP35. The instant application does not disclose the biological role of hRUP35 or its significance. The utilities are not considered to be specific and substantial because the specification fails to disclose any

particular function or biological significance for the hRUP35 of the instant invention. The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After further research, a specific and substantial credible utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, applicants claimed invention is incomplete.

First, what is the specific disorder or dysfunction that is specifically associated with claimed hRUP35. Arguing that hRUP35 is associated with sensorimotor processing and arousal disorders tells the skilled artisan nothing about the specific disorder. The terms sensorimotor processing and arousal disorders are not defined in the specification. There is no disclosure what disorders are encompassed by the terms sensorimotor processing and arousal disorders .

Examiner has interpreted the words sensorimotor, arouse and motor function to mean:

Arouse is to awaken from sleep, to rouse or stimulate to action or to physiological readiness for activity (excite), to awaken from sleep (stir). Sensorimotor means relating to, or functioning in both sensory and motor aspects of bodily activity. Sensor means relating to sensation or to the senses, conveying nerve impulses from the sense organs to the nerve centers.

Motor function: motor means relating to, concerned with, or involving muscular movement.

Based on the definitions motor function, sensorimotor processing and arousal disorders encompass many different disorders, e.g. walking, blinking, balance, inability to sleep, inability to stay awake, inability to keep balance, inability to have an erection, tremors, simple partial epileptic seizure, complex partial seizure, partial with secondary generalized tonic-clonic seizure, absence seizure, myoclonic seizure, tonic-clonic seizure, twitching, Parkinson's disease, inability to move, movement disorders, ataxias, sexual dysfunction etc.. By

simply saying hRUP35 is associated with motor function, sensorimotor processing and arousal disorders tells the skilled artisan nothing about the specific disorder that is result of hRUP35 dysfunction. Will activating the receptor be detrimental or beneficial? Will inhibiting the receptor be detrimental or beneficial? Will the activation of the receptor inhibit a tremor or cause sexual dysfunction? Will the activation of the receptor inhibit a seizure or cause the eye to twitch? Will the activation of the receptor cure Parkinson's disease or cause the person to lose his balance? Further experimentation is required to associate a specific disease or dysfunction with claimed receptor.

The specification discloses " The presence of a receptor in a tissue source, or a diseased tissue, or the presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue, can be used to correlate location to function and indicate the receptor's physiological role/function and create a treatment regimen, including but not limited to, a disease associated with that function/role." In instant case, the presence of the claimed receptor in diseased tissue is not disclosed. The presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue is not disclosed. The presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue and how it can be used to correlate location to function and indicate the receptor's physiological role/function and create a treatment regimen, including but not limited to, a disease associated with that function/role is not disclosed.

The specification discloses, "the receptors can also be localized to regions of organs. Based on the known or assumed roles/functions of the specific tissues to which the receptor is localized, the putative physiological function of the receptor can be deduced. For example and not limitation, proteins located/expressed in areas of the thalamus are associated with motor function, sensorimotor processing and arousal. Proteins expressed in the hippocampus or in Schwann cells are associated with learning and memory, and myelination of peripheral nerves, respectively". The specification discloses

claimed receptor is expressed in the thalamus. All applicants' arguments are based on it being expressed in the thalamus. The claimed receptor is also known today as GPR139. Susens et al (Neuropharamocology, Vol. 50, pages 512-520, 2006) (post filing art) discloses GPR139, as message of around 5.5 kb, was exclusively expressed in the brain and was present strongly in E15 and E17 and very weakly in E11 embryos (Fig. 2A). Two human brain-specific northern blots were assayed with a probe covering nucleotides 295–1035 of mouse **GPR139 and showed predominant expression in putamen, medulla and caudate nucleus. Weaker signals were present in thalamus, amygdala, and spinal cord**. Therefore claimed receptor is not only expressed in the thalamus but also in other areas of the brain suggesting an even broader spectrum of disorders to choose from. It is also important to note that Susens detected two GPR39 variants, in addition to the 5.5-kb band a smaller band of around 3.5 kb was present suggesting differential splicing (Fig. 2B). Applicants do not disclose any splice variants. Susens further discloses GPR139 was most prominently expressed in the brain and in E11, E15 and E17 mouse embryos, and a weak signal was present in mouse testis. These results are in agreement with the data obtained by northern-blot analysis and with ESTs, which documented presence of GPR139 in E12.5–E14.5 eyes, E11 spinal cord and adult mouse brain. In the adult mouse brain intense hybridization signals of GPR139 were restricted to the median habenular nucleus (Fig. 3A, B). In situ hybridization analysis on sagittal sections through murine embryos at E12.5 and E18.5 showed that GPR139 transcripts were detected exclusively in distinct regions of the brain and in spinal cord with slightly increasing intensities towards E18.5 (Fig. 4A, B). GPR139 transcripts accumulated in the CA1 area of the hippocampus and over the median habenular nucleus (Fig. 5D, E), and signals of lower intensity were detected over the lateral habenular nucleus (Fig. 5E). In the midbrain area the nucleus oculomotoris (Fig. 6F) and in the hindbrain the nucleus hypoglossis (Fig. 5L) were highlighted by signals. Lower intensities were detected over the piriform

and enterorhinal cortices (Fig. 5B, F), the lateral septum (Fig. 5B), the amygdala (Fig. 5C), a few median thalamic nuclei, the reticular nucleus of the thalamus (Fig. 5C, D), the central gray (Fig. 5G), the inferior colliculus (Fig. 5G–I), the medial vestibular nucleus and the inferior olive (Fig. 5I, J). Therefore based on the tissue distribution of GPR139 it is impossible to conclusively say what dysfunction specifically results due to claimed receptor dysfunction.

Another potential flaw may be due to interpretation of the data in Figure 2 of the specification. In FIG. 2 of instant application 293 cells were transfected with RUP35 and RUP36 receptor and compared to the control, pCMV. It is concluded that the data indicate that RUP35 receptor is endogenously, constitutively active. RUP35 evidences about a six (6) fold increase in intracellular inositol phosphate (IP3) accumulation when compared to pCMV. Based on this observation applicants conclude that RUP35 increases IP3 in the thalamus. This leap of faith may not be true based on following disclosures:

a) 293 cells are human embryonic kidney cells (see Han et all, Genomics, 87, pages 552-559, 2006), which have not been shown to be a model for thalamus cells. Han discloses changes in cell culture conditions influence the metabolism of cells, which consequently affects the quality of the products that they produce such as recombinant proteins. Depending on the confluence status of the cells certain genes can be up or down regulated (see page 557, column1). In instant case there is no disclosure of the level of transfection or the amount of recombinant protein produced by the cells disclosed in Figure 2. The increased IP3 levels may be due to over expression and have nothing to do with the natural state of the cells in the thalamus as it pertains to expression and second messenger effects of claimed receptor.

b) The type of cell and the GPCR expressed is very important to the effect observed. Susens, discloses, stable expression of GPR139 and another related GPCR, GPR142, was established in the flip-in cell lines CHO-K1 and HEK-293. In both stable cell lines GPR139 was more strongly expressed than GPR142, as shown for CHO-K1 cells in Fig. 6A–F. In HEK-293 cells GPR139 appeared as monomer and in CHO-K1 cells as dimer (Fig. 6G, middle panel). This indicates that a partner or conditions are present in CHO-K1, but not in HEK-293 cells, which favor dimer formation and potential functions. Susens, discloses, "To analyze possible ligands we concentrated on GPR139 because of its higher protein-expression levels and better presentation at the outer cell membrane." Susens shows that the effect of certain effectors in brain extract used to stimulate GPR139 is predominantly mediated by an inhibitory G-

protein. Susens concludes by suggesting, "The presence of GPR139 in brain areas involved in motor control suggests a function as mediator in locomotor activity. Identification of a ligand or of ligands for both receptors may help to clarify their function." Therefore even today the function of GPR139 needs to be clarified. The type of cell used will influence the results obtained because it is still not known if the claimed receptor needs to be present as a dimer to function naturally.

c) Gloriam et al (Biochimica et Biophysica Acta, Vol. 1722, pages 235-246, 2005) disclose GPR139 has a very restricted expression pattern and perhaps reflecting that its functional role is more cell-specific and/or that the expression levels are low. Lower expression levels would suggest lower IP3 levels in the brain. This leads to the question does the skilled artisan activate or inhibit hRUP35 to correct a hRUP35 specific disorder or dysfunction. What ligands will the skilled artisan use to correct this defect, none are known in the art and none are disclosed in the specification.

Therefore the experimental design and the cells used to analyze the GPCR activity greatly influence the results obtained and therefore cast doubt on the interpretation of the results obtained in 293 cells in Figure 2 of instant application and the conclusion that claimed GPCR increases intracellular levels of IP3 being constitutively active. High levels of IP3 in cells expressing abnormal quantities of hRUP35 does not automatically mean constitutively activation and increased IP3 levels in the thalamus based on the observations above. There is nothing in the specification or prior art that suggests that the claimed isolated hRUP35 polynucleotide encodes a dysfunctional polypeptide. This means that the skilled artisan still has to do further research to isolate the dysfunctional gene and determine an associated sensorimotor processing and arousal disorder.

Applicants has presented a laundry list of possible diseases that may be associated with dysfunction of claimed GPCR. They may actually have one that actually results from claimed hRUP35 dysfunction. The question is which one? Defining the disorder by reciting "sensorimotor processing and arousal disorders" provides an unconvincing argument to the office.

The specification discloses diseases and disorders related to receptors located in these tissues or regions include, but are not limited

to, cardiac disorders and diseases (e.g. thrombosis, myocardial infarction; atherosclerosis; cardiomyopathies); kidney disease/disorders (e.g., renal failure; renal tubular acidosis; renal glycosuria; nephrogenic diabetes insipidus; cystinuria; polycystic kidney disease); eosinophilia; leukocytosis; leukopenia; ovarian cancer; sexual dysfunction; polycystic ovarian syndrome; pancreatitis and pancreatic cancer; irritable bowel syndrome; colon cancer; Crohn's disease; ulcerative colitis; diverticulitis; Chronic Obstructive Pulmonary Disease (COPD); Cystic Fibrosis; pneumonia; pulmonary hypertension; tuberculosis and lung cancer; Parkinson's disease; movement disorders and ataxias; learning and memory disorders; eating disorders (e.g., anorexia; bulimia, etc.); obesity; cancers; thymoma; myasthenia gravis; circulatory disorders; prostate cancer; prostatitis; kidney disease/disorders (e.g., renal failure; renal tubular acidosis; renal glycosuria; nephrogenic diabetes insipidus; cystinuria; polycystic kidney disease); sensorimotor processing and arousal disorders; obsessive-compulsive disorders; testicular cancer; priapism; prostatitis; hernia; endocrine disorders; sexual dysfunction; allergies; depression; psychotic disorders; migraine; reflux; schizophrenia; ulcers; bronchospasm; epilepsy; prostatic hypertrophy; anxiety; rhinitis; angina; and glaucoma. Accordingly, the methods of the present invention may also be useful in the diagnosis and/or treatment of these and other diseases and disorders.

Applicants argue that prior art supports Applicants' utility and certainly does not lead one skilled in the art to question it. Applicants have previously argued Salt and Eaton, teach that a GPCR known to stimulate IP3 metabolism modulates sensory response in thalamus, for example response evoked by noxious thermal stimulation of the peripheral receptive field. The specification does not disclose claimed GPCR stimulated IP3 metabolism modulates sensory response in thalamus, or noxious thermal stimulation of the peripheral receptive field.

Knowing the tissue distribution of a GPCR and its second messenger does not automatically mean that its function is known. Claimed GPCR belongs to the Rhodopsin family of GPCR (see Gloriam et al). This is by far the largest of the five human GPCR families and probably the most diverse based on it ligand specificity.

Many members of the Rhodopsin family can be activated by biogenic amines (such as adrenaline, dopamine, histamine and serotonin) and peptides (such as angiotensins, bradykinins, omatostatins, melanocortins, opioids, and galanin). Rhodopsin GPCRs can also be activated by large proteins (such as LH, FSH and TSH), nucleosides and nucleotides (such as adenosine, ATP, UTP and ADP), lipids and eicosanoids (such as eukotrienes, prostaglandins, cannabinoids and free fatty acids) and photons. Moreover, the large group of olfactory receptors belong to this family but two thirds of the 900 genes for olfactory receptors are pseudogenes in humans. Only a few members within this

subgroup are characterized with regard to ligand specificity and hence the majority of olfactory receptors are orphans. The therapeutic potential of most members in this group has, however, not yet been exploited as many of these receptors are still orphans, without known ligand or physiological function. The showing of a relationship to other GPCRs does not necessarily mean that the biological function or ligand can be determined without extensive experimentation.

Gloriam discloses GPR72 is expressed in regions of the hypothalamus, hippocampus and amygdala in both rodents and humans. GPR72 was previously suggested to be a new NPY receptor but experiments showed that it does not bind NPY-receptor ligands in standard binding assays and this receptor is still an orphan GPCR. Therefore tissue specificity can sometimes be meaningless as it pertains to determining physiological function or dysfunction.

Gloriam discloses that the previously orphan GPCRs, GPR40, GPR41 and GPR43 were found to be low affinity receptors to free fatty acids. These receptors have fairly low similarities to other GPCRs and many of their closest relatives bind peptides, except those that bind leukotrienes (the BLTR receptors). Determing the functionality for claimed invention may even be harder because GPR139 pairs with one previously known orphan receptor and it lacks close relatives.

Lee et al. (Expert Opin. Ther. Targets, Vol 6(2), pages 185-202, 2002) discloses one of the most important tasks of modern pharmacology lies in elucidating the functions of GPCRs. Of particular interest are receptors with recognized expression in the central nervous system. Lee also discloses, "The investigation of the physiological and molecular mechanisms of any signal transduction system requires the identity of both ligand and receptor. For this reason, characterization of oGPCRs remains limited until discovery of their endogenous ligands. Prior to discovery of apelin, the apelin receptor was known to be expressed in the CNS and in the periphery, being especially abundant in developing cardiovascular systems with an additional role as a HIV coreceptor in vitro. However, the physiological roles of the receptor were still undetermined for many years. With the identification of the apelin peptide, there is now evidence of several physiological functions, including the modulation of blood pressure, drinking behavior and immune system function" Lee also discloses many examples where the GPCR and its associated G protein are known, therefore the second messenger is also known but extensive experimentation still is required to discover a physiological function. Lee further highlights the problem of assigning function based on tissue specificity by the example on page 194. Lee discloses there remain several somatostatin-like (and closely-related opioid-like) oGPCR, which have yet to be paired with an endogenous ligand. The genes encoding the oGPCRs named GPR7 and GPR8 were both discovered in 1995, shown to be expressed in rat brain in 1999 (GPR7 and GPR8 are both expressed in discrete regions of the brain and GPR8 appears to be species specific, i.e.

absent in rodents) did not bind opioid receptor sub-type-specific compounds or somatostatin. The Lee article was published in 2002, seven years after the discovery of GPR7 and GPR8. Another oGPCR, SALPR, expressed in the brain, particularly in the substantia nigra and pituitary, with some expression in the periphery awaits the identification of its specific endogenous ligand. Therefore determing the physiological function of a GPCR and its endogenous ligand is no easy task, even knowing its tissue specificity.

Applicants present Abstract #328 from the February 2006 Keystone Symposium (enclosed) which discloses GPR139 knock out mice showed impairment of motor function as evaluated by using runway and open field gait analyses, retard, balance beam, and other tests. At two months of age mice showed no impairment in any of these behaviors. At five months of age the mice showed impairment in balance. The conclusion was GPR139 null mutants appear to have a primary age-related balance deficit. Based on this post filing abstract (2006) applicant argues their invention is useful in treating sensorimotor processing and arousal disorders, such as tremor disorder, action tremor disorder, disorders of impaired motor coordination and impaired cognitive performance. Applicants further state, "Thus, the reference clearly substantiates Applicants' position that hRUP35 is associated with such disorders." The results disclosed in Abstract #328 were neither disclosed by applicant or could have been predicted from applicants' disclosure. How does applicants observation that hRUP35 expression in thalamus and increased IP3 levels in 293 cells lead to the prediction that mice lacking hRUP35 would have a balance deficit at five months? Applicants had no way of predicting the function based on the lack of the expression of hRUP35 gene at the time of filing instant application. Further the lack of the polynucleotide in humans has not been determined. A disease state having a dysfunction in hRUP35 that results in a balance disorder in humans has not been shown. Therefore applicant cannot use post-filing art to assert utility on their claimed invention.

Examiner is not disputing that the claimed invention encodes a GPCR but that said GPCR does not have a specific, substantial and credible utility. Although the claimed receptor has been shown to be expressed in the thalamus there is no disclosure of the specific association with a sensorimotor processing or arousal disorder. The determination of the specific association with a sensorimotor processing or arousal disorder requires further research. Unlike the argued agonists of the niacin receptor no agonists or antagonists of RUP35 are disclosed which can be used to support a specific, substantial and credible utility. Again the determination of said ligands and their specific use requires further research. Unlike the niacin receptor agonist, which can be used to raise

HDL levels in man, no agonists or antagonists are disclosed for RUP35 which have a specific use such as raising HDL levels. When the claimed GPCR is compared to Example 12 of Revised Interim Utility Guidelines Training Materials said GPCR has no specific disclosed function or specific ligands that can be used to support utility. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the claimed hRUP35 further experimentation is necessary to attribute a utility to the claimed hRUP35. The instant application does not disclose the biological role of hRUP35 or its significance. The utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the hRUP35 of the instant invention. The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After further research, a specific and substantial credible utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, applicants claimed invention is incomplete.

Therefore the claims are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

Applicant has classified the GPCR of SEQ ID NO:15 encoding the polypeptide of SEQ ID NO:16 into the superfamily of GPCRs. The specification discloses the GPCR of SEQ ID NO:16 can be used to identify test compounds which bind said receptor and treat diseases associated with hRUP35 dysfunction. The GPCR of SEQ ID NO:16 is disclosed is to be involved in a variety of unrelated disease states. It noted that neither the **specific** activity of GPCR of SEQ ID NO:16 or the **specific** treatable disease associated with the GPCR of SEQ ID NO:16 is disclosed. Ligands that bind or activate said GPCR are not disclosed. In light of the specification the skilled artisan cannot come to any conclusions as to the function of the hRUP35 polypeptide or its encoding

polynucleotide. The utility of claimed hRUP35 cannot be implicated solely from homology to the proteins known in the art or from its expression pattern because the art does not provide teaching stating that all GPCRs found in the thalamus have the same activity, same effects, the same ligands and are involved in the same disease states. In light of the specification and art the skilled artisan cannot come to any conclusions as to the function of claimed polynucleotide or its encoded protein. There is no disclosure provided within the instant specification on what specific function the protein of SEQ ID NO:16 possesses, or how to use compounds that bind said protein. No disease states are disclosed that are directly related to hRUP35 polypeptide dysfunction.

The specification fails to disclose, what specific disease is associated with claimed receptor dysfunction or what drugs affect a specific claimed receptor function. The GPCR may have utility in the future, when it has been further characterized (e.g. its dysfunction or function correlated with a disease state) and its ligand characterized. The inclusion in the family of G protein coupled receptors (GPCR) does not constitute either a specific and substantial asserted utility or a well-established utility for that particular GPCR or protein. This is analogous to all proteins or GPCRs can be used as protein markers on a gel.

Specification discloses claimed receptors are useful in screening but the specification does not disclose what claimed receptor specifically regulates and what specific disease the receptor is a target for. What would be the use of using the claimed receptor on a panel for drug screening? The receptor has no known ligand or known function. How would one use the compounds that interacted with said orphan receptors? The specification provides a diverse list of disease states that may be involved in receptor dysfunction. It is unpredictable what ligands will bind to orphan receptors, and further the functional effects of ligand binding may remain uncertain even after extensive experimentation. What is the utility for a ligand, in many cases with no known function, that binds to a receptor of no known function? The ordinary artisan can only speculate on the utility for the ligand and receptor. A utility to orphan receptor cannot be assigned without

knowledge of what disease is associated with claimed receptor dysfunction or what drugs/ligands affect a specific claimed receptor function. Members of a sub-family of G-protein-coupled receptors are also highly divergent in their effects, as highlighted by Murdoch et al (Blood, Volume 95, No.10, pages 3032-3043, 2000), in the discussion of cytokine G-protein-coupled receptors. The utility of claimed receptor cannot be implicated solely from homology to known G-protein coupled receptors or their protein domains because the art does not provide teaching stating that all members of family of G-protein coupled receptors must have the same effects, the same ligands and be involved in the same disease states, the art discloses evidence to the contrary. The specification has not even used protein domains/homology to predict the activity of the protein. Murdoch discloses the superfamily of G-protein-coupled receptors are highly divergent in their effects and include receptors for hormones, neurotransmitters, paracrine substances, inflammatory mediators, certain proteinases, taste and odorant molecules, and even photons and calcium ions. Further, the G-protein that interacts with the claimed orphan receptor and is required for the signal transduction activity is unknown. Watson (The G-Protein Linked receptor Facts Book, pages 2-6 and 223-230, 1994) states **"it has therefore not been possible to identify consensus amino acid sequences that confer G-protein specificity, and thus G-protein interactions cannot be predicted from the primary amino acid sequence"**. Therefore the disclosure of Watson predicts, using the primary structure of the G-protein coupled receptor the skilled artisan cannot predict its associated G-protein or its ligand. G-protein coupled receptors are highly specialized and ligand specific proteins. The superfamily of seven transmembrane domain G-protein coupled receptors are specialized proteins designed for chemical recognition of ligands and subsequent transduction of information encoded in those ligands to the machinery of the cell, and the G-protein coupled receptors interact with alkaloids, biogenic amines, peptides, glycoprotein hormones, light and odorants (Terry Kenakin, Pharmacological Reviews, Vol. 48, No.3, pages 413-462), see page 413.

Kenakin also states, "To achieve information transfer, the ability to bind ligands to a recognition domain and allosterically transmit the presence of that ligand to an intracellular domain appears to be a specialized feature of 7TM receptors. The very properties that define receptors as such also impart unique protein behaviors to receptors, and these behaviors, in turn, affect drug activity", page 414, column 1, second paragraph. Bork (Nature Genetics, Vol. 18, pages 313-318, 1998) provide a review article disclosing the problems of using homology detection methods to assigning function to related members of a family. Bork discloses: a) "While current homology detection methods can cope with data flow, the identification, verification and annotation of functional features need to be drastically improved", page 313, column 1, Abstract, b) there are two bottle necks that need to be overcome en route to efficient functional predictions from protein sequences, i.e., "First, there is the lack of a widely accepted, robust and continuously updated suite of sequence analysis methods integrated into coherent and efficient prediction system. Second, there is considerable 'noise' in the presentation of experimental information, leading to insufficient or erroneous function assignment in sequence databases", page 313, column 1, third paragraph, c) **"In-depth analysis of protein sequences often results in functional predictions not attained in the original studies"**, page 313, column 2, last paragraph, d) **"However, more often than not, it is clear that the cellular role of the protein in question differs from that of the detected homologue(s) and there is currently no automatic means to establish how much functional information can be legitimately transferred by analogy from homologue to the query"**, page 315, column 2, last paragraph, e) pertaining to predictions of protein function, "Do not simply transfer functional information from the best hit. The best hit is frequently hypothetical or poorly annotated; other hits with similar or even lower scores may be more informative; even the best hit may have a different function", while "many proteins are multi functional; assignment of a single function, which is still common in genome projects, results in loss of information and outright errors" and "It is typical that

the general function of a protein can be identified easily but the prediction of substrate specificity is unwarranted; for example, many permeases of different specificity show approximately the same level of similarity to each other", page 316. Karp (Bioinformatics, Vol. 14, No.9, pages 753-754, 1998) has disclosed the problems of using functional prediction based on homology analysis. Karp states, a) "Although we know the accuracy with which sequence homologs can be determined, we know little about the accuracy of the overall process of assigning function by homology, page 753, column 2, second paragraph, b) "We have more faith in the correctness of those sequences whose functions we determined experimentally, rather than through computational means, page 753, column 2, last paragraph, c) "research is required to estimate the error rate of functional annotation by different methods of computational sequence analysis", page 754, column 2, last paragraph. Bork (Current Opinion in Structural Biology, Vol. 8, pages 331-332, 1998), discusses the problems with deriving biological knowledge from genomic sequences and states, "structural similarity does not lead to iron-clad functional predictions" page 331, column 2 last paragraph, "Structural similarity does not necessarily mean a common evolutionary origin" page 332, column 1, second paragraph, and **"Today, what we predict from sequences is at best fragmentary and qualitative"**, page 332, column 2, second paragraph.

Based on the art, the limited homology of claimed GPCR to other proteins cannot be used to predict its function. The following articles are also cited as evidence for the unpredictability of determining a function or ligand of claimed invention based on homology of GPCRs. Further there is the even greater unpredictability of using the claimed invention to treat a disease related to hRUP35 dysfunction.

Civelli et al (Civelli et al, Pharmacology and Therapeutics, November 8, pages 1-8, 2005) discloses that all 7 transmembrane receptors are not GPCRs (page 2, column 1). GPCRs are activated by a plethora of transmitters and have a broad spectrum of interactions. **The role of GPCRs in various tissues may**

be different although the second messengers that result from its initial activation are probably the same. Most GPCRs started as orphan receptors and the discovery of new members found by homology screening suffers from one obvious problem, the receptors found lack their pharmacological identities, their natural ligands (gage 2). **The pursuit to unravel their identities has led to fishing expeditions. The number of orphan GPCRs has steadily increased and at this time the GPCRs outnumber the known potential ligands.** Researchers utilize orphan receptors as baits to isolate their natural ligands, which is meant to identify novel transmitters (page 3). Civelli also discloses the discovery of the natural ligand is no easy task, and specifically states, "GPCRs have been depolarized at a rate of 7-8 per year from 1999 until 2004. This was mostly the result of large-scale random screening of practically all molecules known to exist in cell", (page 4, column 2). There is no rule for predicting the affinity constant of a natural ligand at a particular receptor. The level of receptor expression in a transfected cell can affect ligand potency and is subject to artifacts. Belonging to a family of GPCRs does not insure that all members will bind the same ligand or have the same effects. The recently discovered Mas-related GPCRs, orphan receptors, bind a variety of structurally divers transmitters (ligands), Rfamide peptides for some mouse Mrgs and cortistatin for two human Mrgs, adenine for rat Mrg and beta-alanine for an Mrg found in human, rat and mouse (column 2, page 5). The matched transmitters are specific to particular Mrgs and activate them efficiently. By the mid-1990s approximately 90 transmitters were known, since then, a dozen new transmitters have been found and it is expected that the remaining 120 orphan GPCRs will lead to the discovery of at least 50 more transmitters (page 6, column 1). **There is no doubt that orphan GPCRs are used as potential drug targets but there is no marketed drug directed at any of the ones that have been depolarized since 1995** (page 6, column 1). **Many targets even when recognized of therapeutic interest have showed no value for drug screening** (table 2).

Hancock (Hancock, A.A., Biochemical Pharmacology, Vol. 71, pages 1103-1113, 2006) discloses although histamine H3 receptor (GPCR) was identified pharmacologically in 1993, and despite widespread pharmaceutical interest in the target, no compound interacting specifically with this site has undergone successful clinical examination to develop the necessary proof-of-concept data. The pharmacological effects of known H3 ligands are complex and diverse, since these agents may act both as agonists and antagonists in different systems. Moreover, other compounds show inverse agonism in some models but neutral antagonistic activity in others (see abstract).

Feng et al (Feng et al., Kidney Research, May, Vol. 67, Issue 5, pages 1731-1738, 2005) discloses the heterogeneity for a GPCR AT2 receptor in both ligand binding and induction of arachidonic acid release. The AT2 receptor exhibits distinct biochemical and biological properties compared to its highly homologous orthologues (91% homologous in overall amino acid sequence) of rat, mouse and human. The reducing agent DTT inactivates the rabbit othhologue but potentates the others in ligand binding. Rabbit AT2 receptor but not the other orthologues, induces arachidonic acid release in various cell systems when stimulated with Ang II and CGP42112A, the peptide antagonist. Mutagenesis studies and sequence analysis further indicate that residues His106, ASP188 and Thr393 are responsible for DTT inactivation and residues Val209 and Val249 are partially responsible for arcchidonic acid release (see Abstract)

Marchese et al (Marchese et al., TIPS, Vol. 20, pages 370-375, September 1999) discloses the search for novel GPCR genes (cloning by low stringency hybridization to cDNA/genomic DNA libraries) has far outpaced the identification of novel endogenous ligands, more than 80 orphan GPCRs are awaiting a ligand. Many orphan GPCRs are found to be similar to known GPCRs. Where the identity reaches the threshold of approximately 45% it is likely that the receptors will share a common ligand but **this rule is not without exception** (page 371, column 1)). For example the orphanin RQ/nociceptin

receptor (has approximately 65% amino acid identity to opioid receptors but does not have high affinity for opioid peptides). **Many GPCR subtypes have less than 40% amino acid identity, in which case sequence comparison might not be profitable.** Moreover because the ligand-binding pocket has not been described fully for any receptor, it is not feasible to predict ligand identity. There are no signature amino acids that predict either the nature of the ligand or the identity of the interacting Galpha subunit type(s) (page 371). **Further, the elusive nature of certain labile natural agonists could be a significant hindrance to the discovery of orphan ligands, as there is no reason to believe that the remaining orphan GPCR ligands will all prove to be peptides.** Recently, new complexities have added to the general approach to studying orphan GPCRs. The efficient binding of a ligand to the receptor may require the co-expression of a co-factor protein, e.g. receptor activity modifying protein 1 (RAMP1) in case of amylin binding to orphan GPCR calcitonin receptor-like receptor. Heterodimerization of two subunits may be required for formation of a functional receptor, e.g. GABAb receptor (page 374). The characterization of some GPCR might be more complex than expected, perhaps indicating that functional assays should begin to include co-expression of related orphan GPCRs.

Vanti (Vanti et al., Biochemical and Biophysical Research Communications, Vol. 35, pages 67-71, 2003) discloses the **sequence of a receptor does not necessarily provide insights into the nature of its cognate ligand and therefore such receptors are termed orphan GPCRs**. Vanti, further discloses while some GPCRs, e.g. GPR133 and GPR134, may be nearly identical (95%) they are expressed in different CNS tissues suggesting that this family of receptors may have diverse roles in the CNS (page 70, column 1). Further Vanti discloses the efforts to identify and catalog all human GPCR-encoding genes are ongoing, and these efforts have resulted in the identification of entirely novel signaling systems such as apelin, melanin-concentrating hormone, metastin and urotensin (page 70, column). Based on Vanti's

observation it is highly possible that the claimed GPCR may signal through a novel signaling system. The claimed receptor, based on the preceding references could also have a novel natural ligand that as of yet, has not been identified or purified.

Mutations in a receptor can affect function. Vanti et al (Vanti et al., Genomics 82, 531-536, 2003) discloses that null mutations can arise in a GPCR that renders it truncated and non-functional). Therefore, in the case of the Vanti variant the wrong probe would not detect anything. The GPCR may also be present in other tissues than indicated. The method used of detection is very important. For example, Ta-Tung (Ta-Tung et al, Gene, Vol. 278, pages 41-45, 2001) discloses the assay and tissue used is very important in determing the information gleaned. Ta-Tung discloses (page 49, column 2) that although PSGR (a GPCR) RNA could not be detected by northern analysis in total RNA from whole brain tissue, RT-PCR analysis of five human brain tissue analyses of five regions did reveal the presence of PSGR mRNA specifically in the olfactory epithelium and medulla oblongata (Fig. 3). Based on the wide spread distribution of claimed polynucleotide there is insufficient information provided on which to base a utility of using hRUP35 as a marker for a disease state.

Further, the ability of a GPCR to increase second messenger levels of a compound (e.g. calcium, IP3) by interaction with a G protein in a specific cell type does not mean all GPCRs will have the same physiological function. Even if a GPCR (with known function) increases second messenger levels, for example IP3 levels, in a specific cell, the art discloses that another receptor, which also affects IP3 levels, may have a completely different biological function. Cells are exposed to many extracellular stimuli, yet they respond appropriately only to specific signals, often by means of just a handful of intracellular messengers. There is more to specificity than the controlled expression of signaling proteins. Taylor (Taylor et. al., Calcium signaling:IP3 rises... and again, Current Biology, Vol. 11:R352-R353, 2001), discusses these issues at length and state," **Even within a single cell, different receptors may use the same intracellular**

messenger molecule to very different effect", page R352. The ability of GPCRs to interact with other proteins in the cell and the effect of feedback mechanisms allow them to use the same proteins, e.g. Gq proteins in the case of IP3, or second messenger pathways but have very different effects. For example, Taylor (page R352, column 2) discloses that in pancreatic acinar cells cholecytokinin and acetylcholine receptors use the same Gq proteins to stimulate phospholipase C and so trigger Ca2+ release from intracellular stores, yet the patterns of Ca2+ signals they evoke are quite different". Such diversity sits uneasily with mechanisms wholly dependent on Ca2+ regulation of IP3 receptors. The diversity of signal transduction also applies to receptor subtypes. For example, stimulation of one subtype of metabotropic glutamate receptor, mGluR5, evokes Ca2+ spikes via IP3, but stimulation of another subtype expressed in the same cell, mGluR1 depends upon a single Ca2+ transient. The difference depends upon a single PKC phosphorylation site in mGgluR5 (see Taylor, page R354, column 1). The versatility of the signaling mechanism in cells is also discussed by Berridge et al (Berridge et al, The versatility and universality of calcium signaling, Nature Reviews Molecular Cell Biology, Vol. Pages 11-21, 2000). Berridge discloses the versatility of the signaling mechanism is enhanced by having different second messenger mobilizing molecules linked to separate input signals. Therefore in a given cell two separate molecules linked to the same second messenger such as IP3 can have different effects on the cell.

Therefore, references discussed above disclose the unpredictability of assigning a function to a particular protein based on homology, especially one that belongs to the family of GPCRs, which have very different ligand specificity and functions. The discovery of the endogenous ligands will help determine the precise physiological role for each orphan GPCR. As the functions of these novel receptors are uncovered, they could become targets for the development of new pharmacological therapies for diseases not previously considered

amenable to pharmacological therapy, but this requires further research and therefore the invention is not complete.

It can be argued the GPCR of SEQ ID NO:16 is useful tool as a reagent or a molecular target in the diagnosis and treatment of GPCR mediated disorders. All members of the GPCR protein family have a utility in selectively screening of candidate drugs that target GPCRs. However, for a utility to be well established it must be specific, substantial and credible. In this case, as all receptors are in some combination useful in selectively screening of candidate drugs that target GPCRs and in toxicology testing. However, the particulars of screening of candidate drugs, that target GPCR of SEQ ID NO:16, and in toxicology testing are not disclosed in the instant specification. Neither the candidate drugs or toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility, which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to GPCR of SEQ ID NO:16. Because of this, such a utility is not specific and does not constitute a well-established utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed polynucleotide encoding hRUP35 for screening compounds that are a target for GPCR of SEQ ID NO:16 is only useful in the sense that the information that is gained from the assay and is dependent on the effect it has on the protein, and says nothing with regard to each individual member of the GPCR family. Again, this is a utility, which would apply to virtually ever member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Applicants individual GPCR is affected by a test compound in an assay for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed method of using claimed GPCR has no well-established use. The artisan is required to perform further experimentation

on the claimed GPCR itself in order to determine to what use any information regarding this protein could be put.

With regard to diagnosis of disease, in order for a protein/polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well established or disclosed correlation or relationship between the GPCR of SEQ ID NO:16 and a disease or disorder. The presence of GPCR of SEQ ID NO:16 encoded by the polynucleotide of SEQID NO:15 in tissue is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed GPCR and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the GPCR of SEQ ID NO:16 to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the GPCR of SEQ ID NO:16 is either present only in, e.g. cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. over expression). Evidence of a differential expression might serve as a basis for use of hRUP35 as a diagnostic for a disease. However, in the absence of any disclosed relationship between the hRUP35 and any disease or disorder and the lack of any correlation between the claimed GPCR with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. Congress intended that no patent be granted on a chemical compound whose sole utility consists of its potential role as an object of use testing. *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. 101.

Further, hRUP35belongs is a family in which the members have divergent functions based on which tissues the protein is expressed or administered to. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein

families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family. The diversity of the GPCRs has already been described. Without some common biological activity for the family members, a new member would not have a specific or substantial utility when relying only on the fact that it has structural similarity to the other family members. The members of the family have different biological activities, which may be related to tissue distribution, but there is no evidence that the claimed compounds share any one of diverse number of activities. That is, no activity is known to be common to all members. To argue that all the members can be used for drug screening, toxicology testing and diagnosis, is to argue a general, nonspecific utility that would apply to virtually every member of the family, contrary to the evidence. Further, any compound could be considered as a regulator or modulator of tissue in that any compound, if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which will kill cells if administered in a great enough amount, and which would stimulate cells from which these compounds had been withheld, therefore, they could be considered regulators or modulators of tissue. However, use of these compounds for the modulation of tissue would not be considered a specific and substantial utility unless there was some disclosure of, for example, a specific and particular combination of compound/composition and application of such in some particular environment of use.

Without knowing a biological significance of the claimed GPCR, one of ordinary skill in the art would not know how to use the claimed invention in its currently available form in a credible real world manner based on the diversity of biological activities possessed by the GPCR family. Contrast *Brenner*, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient

likelihood that the steroid would have similar tumor-inhibiting characteristics), with *In re Folkers*, 145 USPQ 390, 393 (CCPA 1965) (some uses can be immediately inferred from a recital of certain properties) or *In re Brana*, 34 USPQ 1436, 1441 (Fed. Cir. 1995) (evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility; here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

The assertion that the claimed invention has utility in drug screening, drug development and disease diagnosis, do not meet the standards for a specific, substantial or well-established utility for reasons set forth above. None of the utilities identified have been demonstrated to be specific to the polypeptide of SEQ ID NO:26 . One of ordinary skill in the art must understand how to achieve an immediate and practical benefit from the claimed species based on the knowledge of the class. However, no practical benefit has been shown for the use of the hRUP35. Applicant has failed with respect to hRUP35, has not described the family of GPCRs in enough detail to show, by a preponderance of the evidence, that hRUP35has any substantial use. The record shows that the family of proteins having GPCR domains is diverse, and has such a broad definition, that a common utility cannot be defined. Moreover, the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In *Brenner,* the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPQ at 690. Here, there is no evidence that the claimed isolated compounds have any utility.

For all the above reasons, the disclosure is insufficient to teach one of skill in the art how to use the invention.

The use of the claimed invention for screening assays, drug discovery, and disease diagnosis are not substantial utilities. The question at issue is

whether or not the broad general assertion that hRUP35 might be used for some diagnostic application in the absence of a disclosure of which diagnostic application would be considered to be an assertion of a specific, substantial, and credible utility. For reasons set forth above the disclosure satisfies none of the three criteria *See In re Kirk*, 153 USPQ 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.)

The prior rejection under 101 followed *Brenner v. Manson*. In that case, the absence of a demonstrated specific utility for the claimed steroid compound was not ameliorated by the existence of a demonstrated general utility for the class. Unlike *Fujikawa v. Wattanasin*, where there were pharmaceutically acceptable in vitro results, here, there is nothing other than relatively low levels of sequence homology to a broad and diverse family of proteins having distinct modes of activity, and no disclosed common mode of action. A rejection under 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967). Further since the claimed hRUP35 has no utility, vectors hRUP35 polynucleotide, cell comprising said vector, and methods of its use hRUP35 polunucleotide or its constructs are also rejected for lack of utility.

On a final note Applicants state, oddly, Applicants do not believe that they have ever attempted to assert for hRUP35 based solely on homology to known GPCRs". The homology aspects of the GPCRs are clearly outlined in the specification, for example page 17, first paragraph states, "Receptor homology is useful in terms of gaining an appreciation of a role of the receptors within the

human body." The examiner has argued that that in instant case homology to other known GPCRs does not predict the function of the claimed GPCR.

6. Claims 29, 42 and 44-56 remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the claimed cDNA encoding hRUP35 further experimentation is necessary to attribute a utility to the claimed polynucleotides and fragments thereof.

Claim Rejection 35 USC 112, 1st paragraph (Written Description)

7. Claims 44-56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 44-56 are drawn to an isolated polynucleotide, wherein said polynucleotide comprises a nucleic acid sequence encoding an endogenous human G protein-coupled receptor that is at least 90% or 95% identical to SEQ ID NO:16 and is capable of stimulating intracellular IP3 accumulation in a constitutive manner. Further, claims are drawn to vectors comprising the polynucleotide of claim 45 or 46, recombinant host cell containing said vector and isolated membrane of said recombinant cell.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is identification of any particular portion of the structure the claimed GPCR that must be conserved for the polynucleotide to encode a protein to have 90% sequence identity with SEQ ID NO:16. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNAs that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. The claims recite a broad arbitrary structural relationship between the claimed nucleic acid sequences, either in terms of its nucleotide sequence or the polypeptide encoded, and the single disclosed species of nucleotide sequence and amino acid sequence, respectively. Therefore nucleic acids encoding non-functional or functionally unrelated proteins to hRUP35 are encompassed by the claims. The recited structural relationships are arbitrary since neither the specification nor the prior art discloses any definitive relationship between protein function and % identity or homology at either the nucleotide or amino acid level; and the specification does not describe a single species of nucleic acid that encodes a functional protein that is not either 100% identical to the recited nucleotide sequence or that encodes a polypeptide that is not 100% identical to the recited amino acid sequence.

While one of skill in the art can readily envision numerable species of nucleic acid sequences that are at least a given % identity to a reference

nucleotide sequence and that encode a polypeptide at least a given % identity to a recited reference amino acid sequence, one cannot envision which of these also encode a polypeptide with a specific activity of the protein of SEQ ID NO:16. The fact remains that the actual nucleic acid sequences which encode a protein with a particular activity or the actual amino acid sequences of such a protein *cannot* be envisioned any better when the possible choices are narrowed from all possible sequences to all possible sequences with an arbitrary structural relationship with a known functional sequence. For example, if one skilled in the art were to make a synthetic nucleotide sequence that encoded a polypeptide with 90% identity to the reference amino acid sequence, he would be no more able to say whether it encoded a functional polypeptide than if the nucleotide sequence encoded a polypeptide that was only 10% identical to the reference polypeptide sequence. Nor would he be able to say whether the sequence existed in nature.

To put the situation in perspective, the number of possible amino acid sequences of 100 amino acids in length is 20^{100} (approx. 10^{130}) and the number of possible nucleotide sequences of 300 nucleotides in length is 4^{300} (approx. 4×10^{180}) . The number of possible nucleotide or amino acid sequences that are of a given %identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + \ldots + X^{n-1}L(L-1)(L-2)\ldots(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)\ldots(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, L is the length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence at a given % identity. For a nucleotide sequence, X is 3 (alternate nucleotides); for an amino acid sequence, X is 19 (alternate amino acids).

For a 100 amino acid sequence that is at least 90% identical to a reference sequence of 100 amino acids, the number of possible sequences having 9 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 6×10^{23}. Whereas the number of possible sequences having 10 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1.1×10^{26}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. It can also be shown that N can be approximated by the formula $X^nL^n/n!$, where $n<<L$. Using this formula to approximate N in this example gives a value of 1.7×10^{26}. For a 300-nucleotide reference sequence, the number of possible 300 nucleotide sequences that are at least 90% identical to the reference is approximately 1.6×10^{56}.

In the present case, the reference amino acid sequence, SEQ ID NO:26, is 353 amino acids long, and the reference nucleotide sequence, SEQ ID NO:15 is 1062 nucleotides long. Using the approximation formula, the number of possible amino acid sequences and nucleotide sequences that are at least e.g. 90% identical to the reference amino acid sequence or nucleotide sequence, would be much larger than 6×10^{23} and 1.6×10^{56}, respectively. While limiting the scope of potential sequences to those that are at least e.g. 90 and 95% identical to a reference greatly reduces the number of potential sequences to test, it does not do so in any meaningful way. All of these values greatly exceed the estimated number of atoms in the universe (10^{70} to 10^{90}). Thus, limiting the claims by the recited structural relationships merely reduces the degree of impossibility of making and testing sequences for those which encode a functional protein encompassed by the claims. Therefore, inclusion of the structural relationships in the claim does not distinguish the instant fact situation from those reviewed in *Amgen, Fiers,* and *Regents of the Univ. Calif.*

The specification does not provide any information on what amino acid residues are necessary and sufficient for a functional activity of stimulating Ip3 accumulation in a constitutive manner. The specification also provides no

teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in an active hRUP35 polypeptide that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. Since there are no other examples of proteins that have structural homology with SEQ ID NO:16, it is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. Therefore one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in case to case painstaking experimental study to determine active hRUP35 variants. Consequently, excessive trial and error experimentation would have been required to identify the necessary nucleic acid sequence derivatives encoding a biologically active hRUP35 with an amino acid sequence differing from SEQ ID NO166 since the amino acid sequence of such polypeptides could not be predicted.

The specification discloses only one putative amino acid sequences, SEQ ID NO:16, for a polypeptide having the necessary properties for the disclosed uses, and provides no guidance on obtaining functional polypeptide variants of SEQ ID NO:16 encoded by SEQ ID NO:15 which would be suitable.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 , clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is

required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird,* 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polynucleotides encoding polypeptides comprising the amino acid sequence set forth in SEQ ID NO:16 but not the full breadth of the claims meets the written description provision of 35 U.S.C.j112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1 115).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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